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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,394	09/10/2003	Patrick Mailliet	ST99049G1 US DIV	2263
5487	7590	08/13/2007	EXAMINER	
ANDREA Q. RYAN			JARRELL, NOBLE E	
SANOFI-AVENTIS U.S. LLC			ART UNIT	
1041 ROUTE 202-206			PAPER NUMBER	
MAIL CODE: D303A			1624	
BRIDGEWATER, NJ 08807			NOTIFICATION DATE	
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			08/13/2007	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	Application No. 10/658,394	Applicant(s) MAILLIET ET AL.	
	Examiner Noble Jarrell	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 June 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 22-29,31-36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 22-24 and 277 is/are allowed.
- 6) ☒ Claim(s) 25-26,28,29 and 31-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>6/26/2007</u> . | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Status of Application*

1. The Amendment – After Non-Final Rejection dated 6/26/2007 is acknowledged. All of applicant's arguments have been fully considered.

### Claims Rejections / Objections Withdrawn

#### *Response to Arguments*

2. Applicant's arguments, see page 6, "information disclosure statement" heading, filed 6/26/2007, with respect to references considered in the IDS dated September 10, 2003 have been fully considered and are persuasive. The objection of 4/2/2007 has been withdrawn.
3. Applicant's arguments, see page 7, heading "objections", filed 6/26/2007, with respect to the reference for example 15 not being available have been fully considered and are persuasive. The objection of 4/2/2007 has been withdrawn.
4. Applicant's arguments, see page 7 under 35 USC § 112 heading, filed 6/26/2007, with respect to only quinoline being enabled for the nitrogen-containing aromatic ring and the aromatic ring and diazine as a distribution agent have been fully considered and are persuasive. The rejection of 6/26/2007 has been withdrawn.

### Claim Rejections Maintained

5. Applicant's arguments filed 6/26/2007 have been fully considered but they are not persuasive. Applicants argue that they are enabled for treatment of all forms of cancer through the antitelomerase activity. However this argument is found unpersuasive because of the following reasons.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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7. Claims 26, 28-29, and 31-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of telomerase, fluorescence of the g-quartet, and inhibition for the A549 cell line, does not reasonably provide enablement for treatment of all forms of cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants show testing on page 56 of the specification of prepared compounds to fluoresce the g-quartet, inhibit telomerase, and inhibit cells of the A549 cell line. Of the compounds tested, only example 15 reads on the elected group. Applicants are not enabled for the treatment of all forms of cancer because the A549 cell line is only associated with the lung (Lavelle, F. *Expert Opinion on Investigational Drugs*, 1998, 7(6), 1015-1021, table 2, entry "A549" under "cell line", page 1017). Applicants have not shown testing with any other cell line. Applicants are also not enabled for the compositions of claims 28-29, 32-33, and 35-36.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) *The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to compounds of claim 22 that can fluoresce with g-quartets and inhibit telomerase. Thus, the claims taken together with the specification imply compounds of claim 22 can inhibit telomerase.

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(3) *The state of the prior art and (4) the predictability or unpredictability of the art:*

Compounds of claim 22 are considered novel. However, the state of the art concerning telomerase being involved in all types of cancer is unpredictable. Blasco (*Cell*, 1997, 91, 25-34) reports that "telomerase is essential for telomere length maintenance, it is not required for establishment of cell lines, oncogenic transformation, or tumor formation in mice." (abstract of article, page 25) Blasco supports this finding because, on page 31, she states "A striking finding from this work is that oncogenically transformed telomerase null nude mouse cells with severely shortened telomeres can form tumors in nude mice. To generate a sizable tumor from a single cell in a mouse requires only about 40-50 cell divisions. Yet, mTR<sup>-/-</sup> G6 MEFs that have already undergone over 300 cell divisions in vivo still formed tumors. Thus, while telomerase is activated in mouse tumors in vivo, it appears not to be required for growth during the 40 or more divisions necessary for tumor formation. This raises the question of why telomerase is activated in mouse tumors if it is not essential for tumor growth." Based on Blanco's reasoning, telomeres are not necessarily required for tumor growth / formation, and therefore, the treatment of telomerase does not guarantee a cancer is being treated. Morin (*Journal of the National Cancer Institute*, 1995, 87(12), 859-861) also states that telomerase is an unpredictable target for cancer: "Telomerase fulfills many of the criteria for an ideal cancer target: the almost universal activation in tumors and a nearly ideal development and tissue-expression pattern. What remains is to show that tumors require telomerase for growth and that loss of telomere function will be clinically useful." (page 860, column 2, paragraph 2) In addition, telomerase is not present in all cell lines. Kim et al. (*Science*, 1994, 266, 2011-2015) report on table 2 (page 2013) that telomerase activity is not present in all malignancies, specifically colonic tubular adenomas and colonic polyps. If one attempted to treat either of these cancers by telomerase inhibition, the therapy would not work. Regarding compositions of claims 28-29, 32-33, and 35-36, applicants have not shown any attempt to actually produce compositions comprising compounds of claim 22 and other anticancer agents. One issue with these compositions is

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that the second compound already treats cancer. Do the applicants foresee an unexpected benefit from the combination of the claimed compounds and the additional agent? Take, for example, cisplatin, a platinum derivative. Perry et al. (*Expert Opinion on Investigational Drugs*, 1999, 8(12), 1981-2008) reports that telomerase activity is inhibited by cisplatin (page 1983, column 2, paragraph 2). Related to these compositions, what is the optimum ratio of the claimed compound to the other anticancer agent? What ratios do not work? Without any proof that these compositions are stable, applicants are not enabled for compositions. For claim 36, applicants do not show that the compositions of claim 26, in conjunction with tumor radiation will result in more effective cancer treatment. It is well known in the art that chemotherapy involves radiation of the tumor.

*(5) The relative skill of those in the art:*

One of ordinary skill in the art is a chemist familiar with preparation of the claimed compounds.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for compounds of claim 22 being prepared, fluorescing with g-quartets, inhibiting telomerase, and being cytotoxic to A549 carcinoma cells.

However, the specification does not provide guidance to show that the claimed compounds can treat all cancer cell lines. Applicants have only shown testing against one cell line, A549, which is associated with lung cancer.

*(8) The quantity of experimentation necessary:*

Considering the state of the art as discussed by the references above, particularly with regards to telomerase not being present in all tumor cell lines, the fact that telomerase is not required for tumor growth, the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

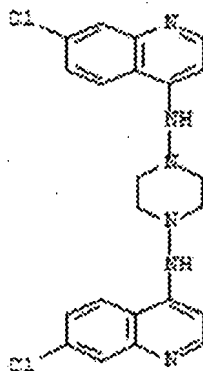
9. Claim 25-26, 28-29, and 34-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25 and 26 are indefinite because "one or more of compounds of claim 22" is/are being administered to a patient. This phrase is broad in nature because it leaves the number of compounds being administered to the patient open. Are 2 compounds of claim 22 being given to the patient? Are three or more drugs compounds being administered to the patient? Applicants never show examples in the specification where two or more compounds of claim 22 are being used to bond g-quartets. Claims 28 and 34 are considered indefinite because one or more compounds of claim 22 are being used in conjunction with another anticancer compound, which may or may not be associated with compounds of claim 22. How many compounds of claim 22 are being used? What is the other anticancer agent? The agent could be one listed in claim 29 or 35, but claims 28 and 34 standing alone are much broader than claims 29 and 35. What is the ratio of compounds in the formulation to one another? Claims 29 and 35 are considered indefinite because the words "derivatives" and "analogues". The terms "platinum derivatives", "cytidine analogues", and "adenosine analogues" are indefinite because the identity of these derivatives and analogues would be difficult to describe and the metes and bounds of said derivatives and analogues applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims. Examples of "platinum derivatives", "cytidine analogues", and "adenosine analogues" are listed in the specification (page 25), but the examples are certainly not limiting.

*Allowable Subject Matter*

10. Claims 22-24 and 27 contain allowable subject matter.

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11. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art is reported by Singh et al. (*Journal of Medicinal Chemistry*, 1971, 14(6), 532-5.), who report the structure shown below.



This structure does not anticipate compounds of claim 22 because halogen is not a valid substituent for the quinoline ring.

### Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.



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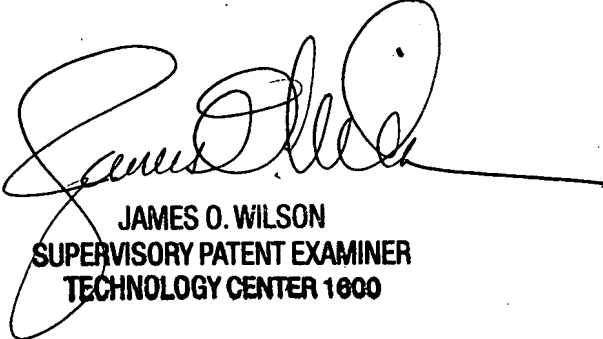
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Noble Jarrell /NJ/

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